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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,520	05/03/2002	Eduardo Mitrani	01/22858	4334

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EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 09/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/009,520	MITRANI, EDUARDO	
	Examiner	Art Unit	
	Wu-Cheng Winston Shen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *17-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application 10/009,520 filed on May 3, 2002 is a 371 of PCT/IL00/00365 filed on 06/22/2000.

Election/Restriction

1. Applicant's election with traverse of Group I, claims 1-16, drawn to a method of inducing angiogenesis in a tissue of a first mammal wherein the method comprises implanting at least one micro-organ for producing a plurality of angiogenic factors, in the reply filed on June 17, 2006 is acknowledged. The traversal is on the ground(s) that a micro-organ is described in the specification as retaining "the basic micro-architecture of the tissues of origin while the same time --- prepared such that cells of an organ explant are not more than 100-450 micros away from a source of nutrients and gases" (page 7, line 5-8). This is not found persuasive because it is stated in the specification "As used herein, the term "micro-organ" refer to organ tissue which is removed from a body and which is prepared, as is further described below, in a manner conductive for cell viability and function. Such preparation may include culturing outside the body for a predetermined time period" (page 6, lines 20-24). The definition of "micro-organ" provided on page 6 does encompass a single cell despite of the preferred embodiments further limiting the characteristics of micro-organ described on page 7 of the specification.

The requirement is still deemed proper and is therefore made FINAL.

Claims 17-36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Applicant timely traversed the restriction (election) requirement in the reply filed on June 17, 2006.

Status of claims: Claims 1-16 are currently under examination.

Claim Rejection - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method, as an experimental system for studying angiogenesis, of inducing angiogenesis in a mouse (or a rat), by implanting the said mouse or rat subcutaneously a syngeneic mouse or rat spleen or lung tissue into cornea, does not reasonably provide enablement for a method of inducing angiogenesis in any mammal by implanting said mammal with micro-organs derived from any tissue of any mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. With regard to the intended therapeutic use of the method encompassed by the claims, there is a total lack of enablement (See further discussions below, under *The state of the prior art*).

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as

routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The nature of the invention: The nature of the instant invention is a cell/micro-organ mediated transfer of gene expression method of inducing angiogenesis in a tissue of a mammal, the method comprising the steps of implanting at least one micro-organ within the tissue of the mammal, and at least one micro-organ being for producing a plurality of angiogenic factors and thereby inducing angiogenesis, wherein said at least one micro-organ is cultured outside the body to retain viability, and in one embodiment said micro-organ is introduced of at least exogenous polynucleotide sequence selected for regulating angiogenesis.

The breadth of the claims: Claim 1 and its dependent claims 2-16 encompass a method of inducing angiogenesis in any tissue of any mammal by implanting anywhere in the said mammal with micro-organs derived from any tissue of the mammal, wherein at least one micro-organ is cultured outside the body to retain viability for any period of time greater than four hours, wherein in one embodiment said micro-organ is introduced with any number of exogenous polynucleotide sequences expressing any protein regulating angiogenesis. The intended uses of the claimed method include therapeutic application of the method in treating diseases comprising ischemia, and using the method as an experimental system to investigate the mechanistic aspects of angiogenesis.

The state of the prior art: With regard to cell/tissue transplantation, Tran et al., reviewed autologous cell transplantation and cardiac tissue engineering stated, "The promising concept of cell transplantation and cardiac tissue engineering has been developed in the last few years and focused on strategies attempting to replace dysfunctional, necrotic, and/or apoptotic cardiomyocytes with new cells of mesodermal origin. Transplantation of autologous cells minimizes the risk of neoplasia and avoids immune rejection associated with allogenic or xenogenic cells and recent data hold enormous hopes for short-term clinical practices. Tissue engineering represents another promising approach that makes possible the creation of new functional tissues to replace the lost or failing one. Three-dimensional polymeric scaffolds provide the mechanical support for the candidate cells until the formation of cardiac-like tissue prior to surgical repair of the infarcted myocardium. For ultimate clinical applications, further investigations have to select the appropriate cell types, to determine the sufficient number of

grafted cells and to provide the long term evaluation of these strategies in the global improvements of cardiac function (neoangiogenesis, synchronous contraction and extracellular matrix remodeling) (See abstract, Tran et al., Autologous cell transplantation and cardiac tissue engineering: potential applications in heart failure. *Biorheology*. 40(1-3): 411-5, 2003).

With regard to implanting cell/tissue for stimulation of angiogenesis in a recipient (claims 1-16), angiogenesis (the formation of new blood vessels) is essential for the growth of new tissue, tissue repair and would healing. Tissue engineering, the construction of new tissue and organs for reparative purposes, relies on angiogenesis for the vascularisation of these new grafts. Cassell et al. reviewed the vascularisation of tissue-engineered grafts stated, "The satisfactory neo-vascularisation of tissue-engineered constructs remains the single largest restraint on the generation of three-dimensional structures", and " Cellular manipulation has moved on from defined-lineage cells to the expansion of embryonic, mesenchymal and haematopoietic stem cells. The isolation and delivery of these cells, with correct differentiation and growth factors, is an area of intense investigation at present (See page 603, right column, first and third paragraphs, Cassell et al., Vascularisation of tissue-engineered grafts: the regulation of angiogenesis in reconstructive surgery and in disease states, *Br. J. Plast. Surg.* 55(8): 603-10, 2002). Cassell et al. further stated, "In therapeutic angiogenesis, the stimulation of angiogenesis by vascular growth factors has shown excellent results in experimental and clinical settings. However, the long-term effects of such treatments are not known (See conclusion, page 609).

With regard to introduction of exogenous polynucleotide sequence into cell/tissue for regulating angiogenesis (claims 11-16), Khurana et al. reviewed gene therapy for cardiovascular

disease stated, "The ability of gene disruption and gene delivery to alleviate patho-physiological changes in diverse animal models of cardiovascular diseases is now well documented. At present, however, neither interference of target gene expression nor the transfer of therapeutic genes is used clinically for cardiovascular disease, and the biggest challenge remains to translate basic experimental findings into clinical benefits" (See conclusions on the right column, page 1214, Khurana et al., Gene therapy for cardiovascular disease: a case for cautious optimism, *Hypertension* 38(5): 1210-6, 2001). Moreover, Laham et al., reviewed gene transfer for angiogenesis in coronary artery disease stated, (1) "Although a tremendous amount of investigation has been performed to design and perfect gene-transfer vectors and even more work has gone into identifying potential target molecules for gene transfer, the question of optimal delivery has scarcely been explored. The vasculature and the myocardium are among the easiest targets for gene transfer because of their accessibility and the need for only transient expression. Although it was thought that getting the vector in contact with its target would be sufficient, a whole series of steps were being taken for granted. The vasculature and the myocardium are subject to rapid blood flow, which leads to washout of the vectors after only a brief period of contact with target cells. Intracoronary delivery results in significant systemic recirculation, exposing non-target organs to the vector" (See page 489, third paragraph), (2) preclinical studies using both plasmid and adenoviral-based gene transfer of FGFs and VEGFs demonstrated functionally significant angiogenesis in various in vitro and in vivo models. These encouraging results have prompted clinical investigations of these gene-transfer strategies in patients with ischemic heart disease who are not candidates for percutaneous coronary intervention or coronary artery bypass surgery. These trials should be interpreted cautiously

because of their uncontrolled, open-label design and a significant placebo effect seen in patients with end-stage coronary artery disease (See page 493, third paragraph), and (3) "Furthermore, it is important to emphasize the potential for these therapeutic agents and gene transfer vectors to result in pathological angiogenesis, as well as the potential for other serious adverse events including death, severe inflammatory reactions, dangerous ventricular tachyarrhythmias, and other unforeseen side effects (See page 494, last paragraph, Laham et al., Gene transfer for angiogenesis in coronary artery disease, *Annu. Rev. Med.* 52: 485-502, 2001).

The predictability or lack thereof in the art: As discussed in the proceeding section, at the time of filing of instant application, there is a lack of predictability in therapeutic angiogenesis gene therapy and cell-based gene transfer for treating angiogenesis related diseases, including coronary artery disease. The claimed novelty of instant invention is focused on the implanting a "micro-organ" into a desired tissue of a mammal, with the intention of overcoming the deficiency of balanced network of growth factors involved in the process of angiogenesis. However, the lack of predictability with regard to issues comprising (1) host inflammatory reactions to an implant micro-organ, rejection of implant when a micro-organ derived from any mammal to any mammal (including rejection due to transplantation of allogenic or xenogenic cells), (2) effects on the induced angiogenesis due to the genetic makeup of recipients and donor mammal of implant, (3) the location of which an implant being planted into the recipient mammal, and tissue and species specificity of and implant in term of the duration of implant survival in a recipient mammal, (4) achieving the expression of plurality of angiogenic factors from donor implant (i.e. micro-organ), including the choice of delivery vector, promoter for

expression, and tissue specificity with regard to the location of implant, and (5) maintaining the viability and genomic stability of any cultured micro-organs will prevent any skilled artisans to make and use the claimed invention without undue experimentation.

The amount of direction or guidance: The specification, particularly under example 1, provides more general materials and experimental methods. More specifically, the specification describes implanted micro-organs induce angiogenesis (page 24), micro-organs transcribed a sustained and dynamic array of angiogenic growth factors when cultured (page 25), implantation of micro-organs reverse ischemia in limbs of rats and mice (page 26), and angiography reveals angiogenic activity in micro-organ implanted rats. However, among these listed direction and guidance, convincing statistic analysis is not available (for instance, it's not clear if the claimed subtle but detectable differences in angiography between micro-organ-treated groups and the control groups (page 27, lines 10-12) is physiologically relevant), and there is no clear cause-and-effect relationship demonstrated between implant and induced angiogenesis. Additionally, specific guidance regarding the culturing condition for maintaining the viability and genomic stability of any given micro-organ is not provided in the specification. Moreover, there is no specific direction or guidance with regard to how the presented method can be modified to apply to any numbers of implants from any tissue implanted to any tissue of any mammal encompassed by the claim so that a skilled artisan can make and use the claimed invention without undue experimentation.

The presence or absence of working example: The instant application lists two working examples with regard to micro-organs (example 2 and 3). Specifically, example 2 presents spleen micro-organs implanted into syngeneic mice whereas example 3 presents rat lung micro-organs implanted in the corneas of syngeneic rats. These two examples demonstrate the feasibility of using the method as a system for study the mechanistic aspects of angiogenesis in syngeneic mice or rats. However, it is not clear for any intended therapeutic use by these two examples (e.g. What's the clinical reason for implanting lung micro-organ to corneas?).

In view of the state of the art, the unpredictability in the art, and the lack of specific guidance and working examples in the specification, one of skill in the art would have to perform undue experimentation to make and use the claimed invention as recited in claims 1-16.

Conclusion

3. No claim is allowed.

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Ram Shukla, can be reached on (571) 272-0735. The fax number for TC 1600 is (571) 273-8300. Any inquiry of a general nature, formal matters or relating to the status of this

application or proceeding should be directed to Dianiece Jacobs whose telephone number is (571) 272-0532.

Wu-Cheng Winston Shen

Wu-Cheng Winston Shen, Ph. D.
Patent Examiner
Art Unit 1632

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER